Complete Summary

GUIDELINE TITLE

Diagnosis and treatment of osteoporosis.

BIBLIOGRAPHIC SOURCE(S)

Institute for Clinical Systems Improvement (ICSI). Diagnosis and treatment of osteoporosis. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2008 Sep. 67 p. [179 references]

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Diagnosis and treatment of osteoporosis. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2006 Jul. 64 p.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- February 1, 2008 - Chantix (varenicline): New information has been added to the WARNINGS and PRECAUTIONS sections in Chantix's prescribing information about serious neuropsychiatric symptoms experienced in patients taking this medication.

COMPLETE SUMMARY CONTENT

IDENTIFYING INFORMATION AND AVAILABILITY
DISCLAIMER

SCOPE

DISEASE/CONDITION(S)

Osteoporosis

GUIDELINE CATEGORY

Counseling
Diagnosis
Evaluation
Prevention
Risk Assessment
Treatment

CLINICAL SPECIALTY

Endocrinology
Family Practice
Geriatrics
Internal Medicine
Obstetrics and Gynecology
Preventive Medicine
Rheumatology

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Health Care Providers
Health Plans
Hospitals
Managed Care Organizations
Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

- To increase the evaluation for osteoporosis risk factors in all adults presenting for a preventive visit
- To improve the treatment of patients diagnosed with osteoporosis
- To improve diagnostic and therapeutic follow-up of adults presenting with a history of low-impact fracture

TARGET POPULATION

- Men and women at risk for osteoporosis

- Men and women with suspected or confirmed osteoporosis

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis/Risk Assessment/Evaluation

1. Assessment for and discussion of risk factors for osteoporosis and low-impact fracture
2. Serial height measurements with a stadiometer
3. Assessment of posture
4. Lateral vertebral assessment with dual energy x-ray absorptiometry (DXA) or radiographs of the thoracic and lumbar spine as indicated
5. Measurement of bone mineral density (BMD) as indicated, including bone densitometry screening of women age 65 and older
6. Vertebral fracture assessment (VFA)
7. Laboratory evaluation of patients with osteoporosis to assess for secondary causes of osteoporosis (tests vary depending on patient features)

Prevention/Treatment

1. Lifestyle counseling regarding measures to prevent fractures (exercise, smoking cessation, alcohol restriction, dietary counseling, weight, environmental modification to prevent falls, measures to reduce the impact of falls [such as soft hip protector pads])
2. Vitamin D and calcium supplementation
3. Pharmacologic agents
    - Gonadal hormone therapy (*prevention*)
    - Bisphosphonates (alendronate, risedronate, ibandronate, zoledronate)
    - Selective estrogen receptor modulator (SERM) (raloxifene)
    - Calcitonin (calcitonin-salmon nasal spray)
    - Parathyroid hormone 1-34 (teriparatide)

4. Follow-up bone mineral density testing (with dual x-ray absorptiometry at a central site after pharmacologic intervention to assess changes in bone mineral density

Notes:

- Routine supplementation with the following alternative and complementary agents has either not been studied or not shown benefit for treatment of osteoporosis: phytoestrogens, ipriflavone, natural progesterone, magnesium, vitamin K, eicosapentaenoic acid and gamma-linolenic acid supplementation, and Kampo formulae
- Guideline developers listed and commented on, but did not recommend, the following non-FDA-approved treatments for osteoporosis: (bisphosphonates: etidronate, pamidronate; calcitriol; cholecalciferol; ergocalciferol; nandrolone decanoate; sodium fluoride; tamoxifen; testosterone; tibolone, and strontium ranelate)

MAJOR OUTCOMES CONSIDERED

- Fracture risk (absolute risk, relative risk, and incidence)
- Predictive value of bone mineral density measurements
- Effects of prevention/treatment interventions on bone density, bone loss, bone health, and fracture risk

- Adverse events of medications

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

A literature search of clinical trials, meta-analysis, and systematic reviews is performed.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Key conclusions (as determined by the work group) are supported by a conclusion grading worksheet that summarizes the important studies pertaining to the conclusion. Individual studies are classed according to the system presented below and are designated as positive, negative, or neutral to reflect the study quality.

Conclusion Grades:

Grade I: The evidence consists of results from studies of strong design for answering the question addressed. The results are both clinically important and consistent with minor exceptions at most. The results are free of any significant doubts about generalizability, bias, and flaws in research design. Studies with negative results have sufficiently large samples to have adequate statistical power.

Grade II: The evidence consists of results from studies of strong design for answering the question addressed, but there is some uncertainty attached to the conclusion because of inconsistencies among the results from the studies or because of minor doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from weaker designs for the question addressed, but the results have been confirmed in separate studies and are consistent with minor exceptions at most.

Grade III: The evidence consists of results from studies of strong design for answering the question addressed, but there is substantial uncertainty attached to the conclusion because of inconsistencies among the results of different studies or

because of serious doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from a limited number of studies of weak design for answering the question addressed.

Grade Not Assignable: There is no evidence available that directly supports or refutes the conclusion.

Study Quality Designations:

The quality of the primary research reports and systematic reviews are designated in the following ways on the conclusion grading worksheets:

Positive: indicates that the report or review has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis.

Negative: indicates that these issues (inclusion/exclusion, bias, generalizability, and data collection and analysis) have not been adequately addressed.

Neutral: indicates that the report or review is neither exceptionally strong nor exceptionally weak.

Not Applicable: indicates that the report is not a primary reference or a systematic review and therefore the quality has not been assessed.

Classes of Research Reports:

A. Primary Reports of New Data Collection:

Class A:

- Randomized, controlled trial

Class B:

- Cohort study

Class C:

- Non-randomized trial with concurrent or historical controls
- Case-control study
- Study of sensitivity and specificity of a diagnostic test
- Population-based descriptive study

Class D:

- Cross-sectional study
- Case series
- Case report

B. Reports that Synthesize or Reflect upon Collections of Primary Reports:

Class M:

- Meta-analysis
- Systematic review
- Decision analysis
- Cost-effectiveness analysis

Class R:

- Consensus statement
- Consensus report
- Narrative review

Class X:

- Medical opinion

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

New Guideline Development Process

A new guideline, order set, and protocol is developed by a 6- to 12-member work group that includes physicians, nurses, pharmacists, other healthcare professionals relevant to the topic, along with an Institute for Clinical Systems Improvement (ICSI) staff facilitator. Ordinarily, one of the physicians will be the leader. Most work group members are recruited from ICSI member organizations, but if there is expertise not represented by ICSI members, 1 or 2 members may be recruited from medical groups or hospitals outside of ICSI.

The work group will meet for seven to eight three-hour meetings to develop the guideline. A literature search and review is performed and the work group members, under the coordination of the ICSI staff facilitator, develop the algorithm and write the annotations and footnotes and literature citations.

Once the final draft copy of the guideline is developed, the guideline goes to the ICSI members for critical review.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

The guideline developers reviewed published cost analyses.

For the U.S. population, treatment continues to be recommended for adults with prior hip or vertebral fracture and adults with bone mineral density (BMD) T-score at the spine, hip or radius of less than or equal to -2.5. In addition, it is suggested for patients with BMD T-scores that are low (osteopenic). Treatment is cost effective when the ten-year probability of hip fracture is greater than or equal to 3%, or ten-year probability of any osteoporotic fracture is greater than or equal to 20%.

Universal screening with bone densitometry followed by treatment of those diagnosed with osteoporosis was found to be cost-effective for women age 65. It becomes more cost-effective as women age into their 80s and 90s.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Critical Review Process

Every newly developed guideline or a guideline with significant change is sent to Institute for Clinical Systems Improvement (ICSI) members for Critical Review. The purpose of critical review is to provide an opportunity for the clinicians in the member groups to review the science behind the recommendations and focus on the content of the guideline. Critical review also provides an opportunity for clinicians in each group to come to consensus on feedback they wish to give the work group and to consider changes necessary across systems in their organization to implement the guideline.

All member organizations are expected to respond to critical review guidelines. Critical review of guidelines is a criterion for continued membership within the ICSI.

After the critical review period, the guideline work group reconvenes to review the comments and make changes, as appropriate. The work group prepares a written response to all comments.

Approval

Each guideline, order set, and protocol is approved by the appropriate steering committee. There is one steering committee each for Respiratory, Cardiovascular, Women's Health, and Preventive Services. The Committee for Evidence-based Practice approves guidelines, order sets, and protocols not associated with a particular category. The steering committees review and approve each guideline based on the following:

- Member comments have been addressed reasonably.
- There is consensus among all ICSI member organizations on the content of the document.
- To the extent of the knowledge of the reviewer, the scientific recommendations within the document are current.
- Either a critical review has been carried out, or to the extent of the knowledge of the reviewer, the changes proposed are sufficiently familiar and sufficiently agreed upon by the users that a new round of critical review is not needed.

Once the guideline, order set, or protocol has been approved, it is posted on the ICSI Web site and released to members for use. Guidelines, order sets, and protocols are reviewed regularly and revised, if warranted.

Revision Process of Existing Guidelines

ICSI scientific documents are revised every 12 to 36 months as indicated by changes in clinical practice and literature. Every 6 months, ICSI checks with the work group to determine if there have been changes in the literature significant enough to cause the document to be revised earlier than scheduled.

Prior to the work group convening to revise the document, ICSI members are asked to review the document and submit comments. During revision, a literature search of clinical trials, meta-analysis, and systematic reviews is performed and reviewed by the work group. The work group will meet for 1-2 three-hour meetings to review the literature, respond to member organization comments, and revise the document as appropriate.

If there are changes or additions to the document that would be unfamiliar or unacceptable to member organizations, it is sent to members to review prior to going to the appropriate steering committee for approval.

Review and Comment Process

ICSI members are asked to review and submit comments for every guideline, order set, and protocol prior to the work group convening to revise the document.

The purpose of the Review and Comment process is to provide an opportunity for the clinicians in the member groups to review the science behind the recommendations and focus on the content of the order set and protocol. Review and Comment also provides an opportunity for clinicians in each group to come to consensus on feedback they wish to give the work group and to consider changes needed across systems in their organization to implement the guideline.

All member organizations are encouraged to provide feedback on order sets and protocol; however, responding to Review and Comment is not a criterion for continued membership within ICSI.

After the Review and Comment period, the work group reconvenes to review the comments and make changes as appropriate. The work group prepares a written response to all comments.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Note from the National Guideline Clearinghouse (NGC) and the Institute for Clinical Systems Improvement (ICSI): For a description of what has changed since the previous version of this guideline, refer to Summary of Changes Report – September 2008.

The recommendations for the diagnosis and treatment of osteoporosis are presented in the form of an algorithm with 14 components, accompanied by detailed annotations. An algorithm is provided for Diagnosis and Treatment of Osteoporosis; clinical highlights and selected annotations (numbered to correspond with the algorithm) follow.

Class of evidence (A-D, M, R, X) and conclusion grade (I-III, Not Assignable) definitions are repeated at the end of the "Major Recommendations" field.

Clinical Highlights

- Discuss risk factors for osteoporosis and primary prevention with all patients presenting for routine health visits. (*Annotations #4, 5; Aim #1*)
- Patients with a high pretest probability of low bone mineral density (BMD) and future fracture should have bone density testing to further define their fracture risk. (*Annotation #8, 9; Aims #1, 3*)
- Address pharmacologic options for prevention and treatment of osteoporosis with appropriate patients at risk for or who currently have signs and symptoms of osteoporosis. (*Annotation #13; Aims #2, 3*)

Diagnosis and Treatment of Osteoporosis Algorithm Annotations

1. **All Patients Presenting for a Routine Visit**

   Osteoporosis is the consequence of continued bone loss throughout adulthood, low achieved peak bone mass, or both. The guideline work group recommends maintaining peak bone mass for all patients. To achieve and maintain maximum bone density, patients should have risks for osteoporosis reviewed when they present to their provider offices. In addition to reviewing historical risk factors (discussed in Annotation #5, "Discuss Risk Factors for Osteoporosis and Osteoporotic Fracture"), it is important to record accurate serial height measurements with a stadiometer and observe posture for kyphosis. Patients with significant acquired kyphosis and/or a historical height loss greater than 4 cm, (1.6 inches) or measured height loss greater than 2

cm (0.8 inches) should have lateral vertebral assessment with dual energy x-ray absorptiometry (DXA) or thoracic and lumbar spine radiographs and bone density testing *[R]*.

2. **Patient With a Low-Impact Fracture**

   Key Points:

   - Low impact fracture defines osteoporosis and requires therapy.

   Discuss osteoporosis risk with any adult who has a history of a low-trauma fracture that may be related to osteoporosis. For the purpose of this guideline, a low-impact fracture will be defined as a fracture occurring spontaneously or from a fall at a height no greater than the patient's standing height. This includes fractures from activities such as a cough, sneeze, or abrupt movement (e.g., opening a window), and patients who have vertebral compression fracture documentation on radiographs regardless of their degree of symptoms. Many adults do not realize that having one fracture in their adult lifetime indicates an increased risk of future fractures, especially in the first few years following the fracture, and may be an indication for bone density testing. This historical risk factor provides information that may be additive to bone mineral density information. The occurrence of a fracture, particularly in the limbs, is followed by accelerated bone loss, not completely reversible, which could lead to an increased risk of subsequent fracture. And, there may be mechanical influences caused by having had one fracture that increase subsequent risk by altering balance and increasing fall risk *[B]*.

   Post-Fracture Recommendations

   - Consider all adults with a history of vertebral fracture, hip fracture, proximal humerus, ankle, pelvis, or distal forearm fracture at higher than average risk for a future fracture.
   - Review lifestyle risk factors for osteoporosis. Discuss adequacy of total calcium and vitamin D intake. Address home safety, fall prevention, and specific exercises for muscle strength.
   - Consider bone density testing in fracture patients willing to accept treatment.
   - Consider all men* and postmenopausal women with low impact fracture as potential candidates for pharmacologic and physical medicine treatment.
   - Women over age 70 with prior fracture are candidates for osteoporosis therapy even without bone density testing.

   *Although the best data available is on postmenopausal women, there may be a similar risk in men, and the guideline work group is including men in this guideline recommendation *[C]*.

   Refer to the original guideline document for more information.

3. **Patient On Chronic Glucocorticoid Therapy or Transplant Recipient**

Key Points:

- Glucocorticoid therapy compounds fracture risk beyond that as determined by BMD.

Glucocorticoid Therapy

Osteoporosis prevention and treatment measures and bone mineral density testing should be considered for anyone who is started on or has been on exogenous glucocorticoid therapy (at a dose of more than 5 mg prednisone or equivalent per day for 3 or more months). Osteoporosis prevention measures should also be considered for those who have been or can be expected to be on a daily high-dose inhaled glucocorticoid for several years. While it is never too late in the course of glucocorticoid therapy to prevent or treat osteoporosis, it is preferable to start preventive measures against bone loss when glucocorticoid therapy is started for two reasons. First, the greatest amount of bone is lost during the first several months of glucocorticoid use. Second, the risk of fracture at any given level of bone mineral density is greater in those on chronic glucocorticoid therapy than in those who are not on a glucocorticoid. That is, fracture risk is disproportionately increased in those with glucocorticoid-induced low bone density relative to those with low bone density associated with the aging process and/or the postmenopausal state *[M]*.

Refer to the original guideline document for information on bone mineral density loss and fracture associated with oral and inhaled glucocorticoids.

Organ Transplantation

Solid organ transplantation of all types and allogeneic bone marrow transplantation are associated with rapid bone loss after transplantation. In addition, many patients develop significant bone loss before transplantation *[R]*.

Refer to the original guideline document for more information on pre- and post-transplantation bone loss.

4. **Discuss Primary Prevention of Fractures**

Key Points:

- Healthy lifestyle discussion at routine visits is important for osteoporosis prevention.

Body Habitus

Low BMI (less than 20) is a strong independent risk factor for osteoporosis and fracture. Weight less than 127 pounds, associated with small bones, is a risk factor for osteoporosis *[B]*. Primary prevention should include counseling patients on achievement and maintenance of a healthy body weight (BMI between 20 and 25). A balanced diet including dairy products and appropriate

nutrition should be discussed with patients *[B]*. Also see Annotation #5, "Discuss Risk Factors for Osteoporosis and Osteoporotic Fracture."

Gonadal Hormonal Status

Women who are prematurely hypogonadal and hypogonadal men who are at increased risk for fracture should be considered for replacement therapy. For further information, please see Annotation #12, "Consider Secondary Causes/Further Diagnostic Testing" as well as Annotation #13, "Address Options for Prevention or Treatment of Osteoporosis."

Exercise

Exercise is well known for its many benefits both short-term and long-term. Weight bearing and muscle strengthening exercises have been shown to be an integral part of osteoporosis prevention as well as a part of the treatment process.

Three components of an exercise program are needed for strong bone health: impact exercise such as jogging, brisk walking, stair climbing; strengthening exercise with weights; and balance training such as Tai Chi or dancing.

Refer to the original guideline document for more information.

Smoking Cessation

Smoking cessation counseling should be done at every visit. Discussion can include helpful strategies such as nicotine replacement therapy with patches, gum, etc. Bupropion, varenicline, and available smoking cessation classes may also be discussed. For more information on smoking cessation, please refer to the National Guideline Clearinghouse (NGC) summary of the Institute for Clinical Systems Improvement (ICSI) guideline, Tobacco Use Prevention and Cessation for Adults and Mature Adolescents. Also see Annotation #5, "Discuss Risk Factors for Osteoporosis and Osteoporotic Fractures."

Alcohol Restriction

Limit alcohol use to *no more than* two drinks per day. One drink equals 12 ounces of beer, 5 ounces of wine, or 1.5 ounces of 80-proof distilled spirits. This limit will help to protect bone health and reduce the risk of falls. See Annotation #5, "Discuss Risk Factors for Osteoporosis and Osteoporotic Fractures."

Calcium

Adequate calcium intake from food sources and supplements promotes bone health. When food sources do not provide enough calcium, supplements can be used to meet this goal. Bioavailability of calcium in food sources and supplements is a factor in achieving daily calcium recommendations. See United States Department of Agriculture (USDA) table for foods rich in calcium (http://www.nal.usda.gov/fnic/foodcomp/search).

Some calcium supplement formulations contain lead. Therefore, the United States Pharmacopeia (USP) labels should indicate lead testing *[D]*.

Daily elemental calcium recommendations for healthy individuals from **diet and supplement** include:

- 19-50 years: 1,000 mg
- Over 50 years: 1,200 mg *[M]*
- Maximum limit: 2,150 mg

However, for people with established osteoporosis, glucocorticoid therapy, pregnant or nursing women, or persons over the age of 65, it may be more appropriate to recommend 1,500 mg *[R]*.

Calcium supplementation has been shown to increase the ratio of high-density lipoprotein (HDL) cholesterol to low-density lipoprotein (LDL) cholesterol by almost 20% in healthy postmenopausal women by binding to fatty acids in the gut. Oversupplementation, however, has not been shown to translate into reduced coronary or cerebrovascular events, particularly in the elderly who may have compromised kidney function. Oversupplementation may be associated with an increased risk of kidney stones and vascular calcification *[A]*.

Both low fractional calcium absorption and low dietary calcium intake have been associated with increased fracture risk. Since fractional calcium absorption is affected by multiple factors and decreases with age, adequate lifetime dietary calcium is an important recommendation for bone health *[R]*.

Calcium absorption is compromised when oxalic acid is present in foods such as dark, green, leafy vegetables. An exception is soybeans. A variety of foods with calcium is recommended.

Bioavailability from calcium supplements is affected by meals, dose size and tablet disintegration. Calcium absorption decreases at doses greater than 600 mg; therefore, supplements should be taken with meals and in divided doses. Taking calcium carbonate supplements on an empty stomach may increase the risk of kidney stones. Heavy metal levels in calcium supplements vary, with some supplements exceeding the acceptable level, and absorption of calcium carbonate may be decreased in the environment of high-dose proton-pump inhibitor use or histamine receptor blockers *[A]*, *[D]*, *[R]*.

Calcium slows age-related bone loss. [*Conclusion Grade II, See Conclusion Grading Worksheet A -- Annotations #4 & 5 (Calcium) in the original guideline document*]

Calcium may reduce osteoporosis fracture risk. [*Conclusion Grade III, See Conclusion Grading Worksheet A -- Annotations # 4 & 5 (Calcium) in the original guideline document*]

Vitamin D

Adequate vitamin D intake supports calcium absorption and bone metabolism. Since sunlight exposure cannot be assumed to produce needed vitamin D, dietary sources are essential. Many adults are deficient in vitamin D, and supplements are often needed to meet daily requirements.

Recent studies concerning vitamin D and bone health demonstrate daily vitamin D supplementation in the range of 700-800 international units can decrease hip fracture risk in the elderly by 26% and any non-vertebral fracture by 23% *[M]*.

The effects of optimal vitamin D levels include:

- Maximum suppression of circulating parathyroid hormone (PTH)
- Increased calcium absorption
- Decreased rates of bone loss
- Decreased risk of falling (22%)
- Improved lower extremity functioning *[R]*

The high-risk group (i.e., the elderly, long-term care residents and those with no sunlight exposure) would be expected to receive the greatest benefit from vitamin D supplementation *[R]*.

Target levels for optimum 25-OH vitamin D are 30 ng/mL or 80 nmol/L and often require oral supplementation of 700-1,000 international units. However, most multivitamins contain 400 international units vitamin D, which may be inadequate *[R]*.

Vitamin D_2 (ergocalciferol) is equally effective as vitamin D_3 (cholecalciferol) in maintaining 25-OH vitamin D serum levels when given at 1,000 international units daily *[A]*.

Although milk is the only dairy source of vitamin D, studies have demonstrated highly variable levels of vitamin D fortification in milk in both the U.S. and Canada. Other food sources of vitamin D are affected by the time of year they are harvested *[R]*.

Prevention of Falls

Preventing falls reduces fracture risk. Modifying environmental, personal risk, and medication-related factors can be effective in reducing falls. Home visits may help with this. In addition to vitamin D supplementation, hip protector pads for frail, elderly adults have been shown to reduce hip fractures in some studies, but not in others. Measures to decrease kyphotic posture and improve unsteady gait such as Tai Chi *[M]* can decrease falls.

Please, see Annotation #5, "Discuss Risk Factors for Osteoporosis and Osteoporotic Fracture." Also see ICSI Prevention of Falls protocol.

5. **Discuss Risk Factors for Osteoporosis and Osteoporotic Fracture**

The following are risk factors for osteoporosis and osteoporotic fracture:

- A prior fragility fracture
- Parental history of hip fracture
- Current tobacco smoking
- Long-term use of oral glucocorticoids
- Rheumatoid arthritis
- Secondary causes of osteoporosis*
- Daily alcohol use of three or more units daily
- Advanced age (greater than age 65)
- Body habitus (weight less than 127 pounds; or BMI less than or equal to 20)
- Caucasian or Asian race
- Hypogonadism
- Sedentary lifestyle
- Diet deficient in calcium or vitamin D without adequate supplementation
- Increased likelihood of falling

[R]

*For a list of secondary causes of osteoporosis, please see Appendix A, "Secondary Causes of Osteoporosis" in the original guideline document.

Risk factors for osteoporosis and fractures are fixed or modifiable. Some risk factors for osteoporosis are also risk factors for fracture independent of bone mineral density. They are important to know so they can be assessed and modified if possible.

Advanced age, female gender, Caucasian and Asian race, and hypogonadal states are risk factors for osteoporosis. The only one of these that is modifiable is hypogonadism (with replacement therapy). African-American women have a decreased risk, partly because they begin menopause with a higher BMD and have a lower rate of bone loss after menopause. Besides these, age and prior fracture are also predictors of fracture independent of bone mineral density *[B]*.

Refer to the original guideline document for information on relationship of bone mineral loss with body habitus; family history of osteoporosis; cigarette smoking; sedentary lifestyle; alcohol, calcium, and vitamin D intake; and increased likelihood of falling.

6. **Low Pre-Test Probability of Low BMD and Future Fracture Based on Patient Profile**

The following individuals are at low risk of low bone density and future fracture; bone density testing in general is not recommended:

- Premenopausal women who have not had a fracture with minor trauma, are not on chronic glucocorticoid therapy, do not have secondary amenorrhea, and do not have a chronic disease associated with bone loss

- Eugonadal men less than age 70 who have not had a fracture with minor trauma, are not on glucocorticoid therapy, and do not have any significant additional risk factors associated with bone loss
- Postmenopausal women under age 65 who have been on hormone replacement therapy since menopause and who do not have any significant additional risk factors

[R]

7. **Address/Reinforce Options for Prevention of Osteoporosis**

   Osteoporosis is the consequence of continued bone loss throughout adulthood, low achieved bone mass, or both. Because of this, providers are encouraged to periodically review historical risk factors (see Annotation #4, "Discuss Primary Prevention of Fractures") and primary prevention strategies (see Annotation #5, "Discuss Risk Factors for Osteoporosis and Osteoporotic Fracture") with their patients. Preventive health maintenance exams provide an excellent opportunity for this review.

8. **High Pre-Test Probability of Low BMD and Future Fracture Based on Patient Profile**

   Key Points:

   - Patients can be risk-stratified to determine the appropriateness of bone density testing.

   The following individuals are at sufficiently high risk for low bone mass and future fracture that a bone mineral density test is justified to further define that risk. This assumes that the individual being tested is willing to consider pharmacologic treatment for low bone mass documented on a bone density test.

   - Prior fracture with minor trauma (fall from standing height or less)
   - Those who have been or are anticipated to be on glucocorticoid therapy for 3 or more months at a dose equivalent to or greater than 5 mg prednisone per day
   - Radiographic osteopenia or vertebral deformity consistent with fracture
   - All women 65 years of age or older
   - Postmenopausal women less than age 65 with one of the following additional risk factors:
     - Body weight less than 127 lbs or a BMI of 20 or less
     - History of nontraumatic fracture after age 45 in a first-degree relative
     - Current smoker
     - Not using hormone therapy
     - Surgical menopause, or natural menopause before age 40
   - Chronic diseases known to be associated with bone loss (see Appendix A, "Secondary Causes of Osteoporosis" in the original guideline)
   - Premenopausal women with hypoestrogenic amenorrhea greater than one year
   - Men with hypogonadism more than 5 years

- Prolonged severe loss of mobility (unable to ambulate outside of one's dwelling without a wheelchair for greater than one year)
- Solid organ or allogeneic bone marrow transplant recipient
- Medications for malignancy are likely to cause bone loss in patients
- Bariatric surgery *[C]*

[R]

Refer to the original guideline document for more information.

9. **Recommend Bone Density Assessment**

Key Points:

- BMD measurement with DXA is the single best imaging predictor of fracture risk as well as the best monitor of patient response to treatment.
- DXA is ideally performed by a technologist certified by the International Society of Clinical Densitometry (ISCD) or the American Registry of Radiologic Technologists (ARRT)

Measurements of BMD with DXA can predict fracture risk and allow for the identification of people who are at increased risk of fracture. Reviews of prospective cohort studies and case control studies have documented a direct relationship between decreasing BMD and increasing bone fracture risk. Additionally, there is strong evidence that stabilization or increases in BMD with therapy for osteoporosis are associated with substantial reductions in fracture incidence. Therefore, densitometry offers an objective measurement of a patient's response to treatment over time *[M]*, *[R]*. At this time there are not cost effectiveness data for monitoring response to treatment.

Current practice is to describe an individual's bone mineral density as compared to a reference normal population. In this sense, a T-score is the number of standard deviations above or below the mean for a gender- and ethnicity-matched young adult healthy population. A T-score is calculated from the following equation:

[(measured BMD - young adult population mean BMD) / young adult population SD]

A Z-score is the number of standard deviations above or below the mean for gender-, ethnicity-, and age-matched healthy population. A Z-score is calculated from the following equation:

[(measured BMD - age-matched population mean BMD) / age-matched population SD]

Normal, low bone density (osteopenia) and osteoporosis are defined by the lowest of lumbar spine (at least two evaluable vertebrae required), femoral neck, and total femur T-score, according to the World Health Organization (WHO). The one-third radius site may be used if either the lumbar spine or

femur is non-evaluable. Although the following classifications were originally drafted for Caucasian postmenopausal women, this also applies to men age 65 and older *[R]*.

- Normal: A T-score greater than or equal to -1
- Low bone density (osteopenia): A T-score between -1 and -2.5*
- Osteoporosis: A T-score less than or equal to -2.5
- The term "severe osteoporosis" is reserved for patients with a fragility fracture(s) *and* a low bone density.

* Following a Position Development Conference on bone densitometry in 2005, the International Society of Clinical Densitometry recommends that the term "osteopenia" be retained, but "low bone mass" or "low bone density" are the preferred terms *[R]*.

For patients who decline bone density studies, reinforce osteoporosis prevention.

Z-scores are not used to define osteoporosis. However, a low Z-score identifies individuals with bone mineral densities lower than expected for age *[R]*.

The National Osteoporosis Foundation (www.NOF.org) recommends bone density testing in the following:

- Women age 65 and older and men age 70 and older, regardless of clinical risk factors
- Younger postmenopausal women and men age 50-70 about whom you have concern based on their clinical risk factor profile
- Women in the menopausal transition if there is a specific risk factor associated with increased fracture risk such as low body weight, prior low-trauma fracture, or high-risk medication
- Adults who have a fracture after age 50
- Adults with a condition (e.g., rheumatoid arthritis) or taking a medication (e.g., glucocorticoids greater than or equal to 5 mg/day for three months or longer) associated with low bone mass or bone loss
- Anyone being considered for pharmacologic therapy for osteoporosis
- Anyone not receiving therapy in whom evidence of bone loss would lead to treatment
- Postmenopausal women discontinuing estrogen should be considered for bone density testing

[R]

Universal bone densitometry screening of women age 65 and older and men age 70 and older is now recommended by nearly all specialty societies that have constructed guidelines for the diagnosis and management of osteoporosis, including the United States Preventive Services Task Force *[R]*. Moreover, universal screening with bone densitometry followed by treatment of those diagnosed with osteoporosis was found to be cost-effective for women age 65. It becomes more cost-effective as women age into their 80s and 90s *[D]*.

Refer to the original guideline document for more information regarding the Bone Mass Measurement Act of 1998, peripheral DXA, computed tomography (CT)-based absorptiometry, and quantitative ultrasound densitometry (QUS).

Vertebral Fracture Assessment (VFA)

VFA is broadly indicated when there is a reasonable pretest probability that a prevalent vertebral fracture will be found on the study that would influence management of that patient. The following are reasonable indications for a VFA at the time a bone density test is done:

Postmenopausal women with low bone mass by BMD criteria, PLUS any one of the following:

- Age 70 years or more
- Historical height loss (current height compared to recalled height as young adult) greater than 4 cm (1.6 inches)
- Prospective height loss (current height compared to a previous measured height) greater than 2 cm (0.8 inches)
- Self-reported prior vertebral fracture (not previously documented)
- Two or more of the following:
    - Age 60 to 69
    - Historical height loss of 2 to 4 cm
    - Self-reported prior non-vertebral fracture
    - Chronic disease associated with increased risk of vertebral fracture (chronic obstructive pulmonary disease [COPD], rheumatoid arthritis, Crohn's disease)

Men with low bone mass by BMD criteria, PLUS any one of the following:

- Age 80 years or more
- Historical height loss (current height compared to recalled height as young adult) greater than 6 cm (2.4 inches)
- Prospective height loss (current height compared to a previous measured height) greater than 3 cm (1.2 inches)
- Self-reported prior vertebral fracture (not previously documented)
- Two or more of the following:
    - Age 70 to 79
    - Historical height loss of 3 to 6 cm
    - Self-reported prior non-vertebral fracture
    - Chronic disease independently associated with vertebral fracture
    - On androgen deprivation therapy or status postorchiectomy

Men or postmenopausal women with osteoporosis by BMD criteria for whom documentation of one or more prevalent vertebral fractures would alter clinical management

Women or men with chronic systemic glucocorticoid therapy (prednisone 5.0 mg or more per day for three or more months, or equivalent)

[R]

The advantages of VFA versus standard spine x-rays are convenience, lower cost and markedly lower radiation exposure.

10. **Post-Test Probability**

Key Points:

- BMD test results provide good information in predicting future fracture risk.
- Other historical factors that relate to bone quality augment BMD data in modifying risk.

Fracture risk in an individual patient is defined as the likelihood of sustaining an osteoporotic fracture over an interval of time. Current fracture risk is defined as the likelihood of an osteoporotic fracture in the patient's remaining lifetime years.

Current fracture risk can be expressed in terms of absolute risk, relative risk, or incidence (annual) risk. Absolute fracture risk is the actual risk of fracture for a given patient. Relative risk of fracture is the ratio of the absolute risk of fracture for the patient compared to the absolute risk of fracture for a young adult-, gender-, and ethnicity-matched reference population. Relative risk of fracture is increased by 1.5 to 3.0 times for each 1.0 standard deviation decrease in bone density below the mean for young adults of the same gender and ethnicity. Fracture risk data in elderly postmenopausal women suggest that fracture prediction is nearly equal regardless of the skeletal site assessed or the type of technology used, with the exception that hip fracture risk is best predicted by proximal femoral bone mineral density measurement *[B]*. Similar data are being accumulated for men, although the numbers of studies published so far are much smaller *[B]*, *[C]*.

11. **Is Risk of Fracture Increased?**

Low fracture risk is clinically defined by a bone mineral density T-score above -1.0 (normal bone density by the WHO definition).

Key Points:

- The femoral neck T-score is best used in combination with clinical risk factors to predict a given patient's fracture risk in the FRAX™ model.

Even though osteoporosis is defined by a BMD T-score of less than or equal to -2.5, and low bone density (osteopenia) is defined as a T-score of -1 to -2.5, and the relative risk for fracture is directly correlated to T-score bone density, the absolute risk of fracture is not only related to bone density but also by bone quality and other non-bone density risk fractures for fracture including clinical risk fractures. Therefore, intervention thresholds based on BMD alone lack high sensitivity. The use of clinical risk factors that add information on fracture risk independent of BMD improves sensitivity of assessment. A recent

meta-analysis *[M]* has identified clinical risk factors for fracture that provide independent information with analysis based on primary data from nine prospective population-based studies and subsequently validated in two large cohorts. Independent risk factors include:

- A prior fragility fracture
- Parental history of hip fracture
- Current tobacco smoking
- Every long-term use of oral glucocorticoids
- Rheumatoid arthritis
- Other secondary causes of osteoporosis*
- Alcohol use of three or more units daily

*Secondary causes of osteoporosis consistently documented to be associated with increased fracture risk include untreated hypogonadism in men and women, inflammatory bowel disease, prolonged immobility, organ transplantation, type I diabetes and thyroid disorders. The independence of these from BMD is uncertain.

Using the above data and an ethnicity- and sex-specific database, the World Health Organization has developed a FRAX™ WHO Fracture Risk Assessment Tool that allows prediction of the ten-year absolute fracture risk for hip fracture and all osteoporotic fractures based on femoral neck bone density. In the absence of femoral neck BMD, total hip BMD may be substituted; however, use of BMD from non-hip sites in the algorithm is not recommended because such use has not been validated. The FRAX™ calculation can be found on the Web at www.shef.ac.uk/FRAX/tool.jsp?locationValue=2 and is applicable to adults ages 40 to 90 who have not received prior treatment with osteoporosis medication including bisphosphonates, calcitonin or teriparatide.

For the U.S. population, treatment continues to be recommended for adults with prior hip or vertebral fracture and adults with BMD T-score at the spine, hip or radius of less than or equal to -2.5. In addition, it is suggested for patients with BMD T-scores that are low (osteopenic). Treatment is cost effective when the ten-year probability of hip fracture is greater than or equal to 3%, or ten-year probability of any osteoporotic fracture is greater than or equal to 20%. This is a basic tool that should be used in the clinical context of the patient. For example, patients with significantly lower BMD of the spine than the femur may have risk for vertebral fracture not captured in the model, and clinical judgment should be used regarding the need for treatment despite a lower fracture risk from the FRAX™ calculation *[M]*.

Some patients with very low T-scores will never sustain an osteoporotic fracture, whereas some patients with normal T-scores will have fractures. Patients who fall infrequently are less likely to sustain osteoporotic fractures.

Previous osteoporotic fractures sustained by the patient, history of osteoporotic fractures sustained by the patient's family members, increased rate of bone turnover, the patient's risk of falling, and the use of medications that predispose to falling, also help predict future fracture risk *[B]*.

Bone mineral density is the single best predictor of future fracture. About 80% of the variance in bone strength and resistance to fracture in animal

models is explained by bone mineral density, and numerous studies have demonstrated that fracture risk is predicted by bone mineral density *[B]*.

Patients found to have low risk of future fracture by bone mineral density testing should not automatically be assumed to remain at low risk of future fracture over their remaining lifetime years. Patients should be periodically reassessed by reviewing risk factors for osteoporosis, evaluating current primary prevention efforts, reviewing the clinical history for osteoporotic fractures subsequent to the initial bone density evaluation, and measuring bone mineral density. Clinical judgment must be used in determining the appropriate intervals between repeated measurements of bone mineral density over time. Whenever remeasure occurs, it is important to use the same densitometer. In some patients, such as those expected to have high bone turnover and rapid bone loss due to early postmenopausal status, initiation or continuation of steroid therapy, organ transplantation, or other causes, it may be appropriate to remeasure bone density as soon as 6-12 months after the initial measurement. In those patients not expected to have high turnover or rapid loss, it is appropriate to remeasure bone density at an appropriate interval, such as two to five years after the initial measurement, in order to detect patients who lose significant bone density over time.

12. **Consider Secondary Causes and Further Diagnostic Testing**

Key Points:

- A minimum screening laboratory profile should be considered in all patients with osteoporosis.

At this time there is no consensus about the routine use of serum and/or urine markers of bone turnover in the evaluation of patients with osteoporosis. See the ICSI Technology Assessment Report #53, Biochemical Markers for Bone Turnover in Osteoporosis, for more information.

Certain diseases are commonly associated with bone loss. These diseases are listed in Appendix A, "Secondary Causes of Osteoporosis," in the original guideline document. In broad categories, these include chronic inflammatory autoimmune conditions, endocrinopathies, malignancies, and malabsorptive states.

Consider the following evaluation for the patient with osteoporosis without prior workup:

- A biochemical profile that provides information on:
    - Renal function
    - Hepatic function
    - Calcium (important if starting an antiresorptive or anabolic agent)
        - Elevated in hyperparathyroidism
        - Decreased in malabsorption, vitamin D deficiency
    - Alkaline phosphatase
        - Elevated in Paget's Disease, prolonged immobilization, acute fractures and other bone diseases

        - Phosphorus
            - Decreased in osteomalacia
    - A complete blood count may suggest bone marrow malignancy or infiltrative process (anemia, low white blood cell count [WBC], or low platelets) or malabsorption (anemia, microcytosis, or macrocytosis).
    - An elevated sedimentation rate or C-reactive protein may indicate an inflammatory process or monoclonal gammopathy.
    - Thyroid-stimulating hormone (TSH) and thyroxine
    - 25 hydroxy (OH) vitamin D (optimal level greater than or equal to 30 ng/mL to maximally suppress parathyroid hormone (PTH) secretion)
    - Intact parathyroid hormone
    - The 24-hour urinary calcium excretion on a high-calcium intake screens for malabsorption and hypercalciuria, a correctable cause of bone loss. Low 24-hour urine calcium suggests vitamin D deficiency, osteomalacia, or malabsorption due to small bowel diseases such as celiac sprue.
    - Testosterone (total and free) in men and estradiol (total and bioavailable) in women; luteinizing hormone (LH) and follicle-stimulating hormone (FSH) and prolactin if evidence of hypogonadotropic hypogonadism
    - Tissue transglutaminase if clinical suspicion for gluten enteropathy for low 25-OH vitamin D
    - 24-hour urinary free cortisol or overnight dexamethasone suppression test if clinical suspicion of glucocorticoid excess
    - Serum and urine protein electrophoresis, with a conditional immunoelectrophoresis

    Refer to Appendix A, "Secondary Causes of Osteoporosis" in the original guideline document for a table with the common causes of secondary osteoporosis.

13. **Address Options for Prevention and Treatment of Osteoporosis**

    Key Points:

    - Lifestyle adjustments are universally recommended for bone health
    - Bisphosphonates have the strongest data showing risk reductions in both vertebral and non-vertebral fractures.
    - Adequate calcium and vitamin D intake and regular physical exercise are important for the prevention of osteoporosis, and they play an important role in its treatment.
    - Estrogen is considered first-line therapy for the prevention of osteoporosis in prematurely menopausal women under the age of 50.
    - Anabolic therapy with parathyroid hormone is indicated for patients with particularly high-risk for future fracture, and data shows reduction in vertebral and non-vertebral fracture.
    - Nasal calcitonin is not considered a first-line treatment for osteoporosis, but may be useful in some populations.
    - Selective estrogen receptor modulator (SERM) treatment with raloxifene has shown vertebral fracture risk reduction in postmenopausal osteoporosis.

Please see the medication tables in Appendix B, "Recommended Pharmacologic Agents" of the original guideline document for specific information on pharmacologic agents for treatment and prevention of osteoporosis.

Osteoporosis Prevention (also see Annotation #4, "Discuss Primary Prevention of Fractures")

Estrogen has traditionally been considered first-line therapy in women over 50 years of age for prevention of osteoporosis and in prematurely menopausal women under the age of 50. If the only reason hormone therapy has been prescribed is for osteoporosis prevention, other options should be considered. If the decision is made to discontinue estrogen, a BMD should be obtained to determine if other bone loss prevention therapies are needed. Other medications for prevention include bisphosphonates and raloxifene.

Post-transplantation Bone Loss

Antiresorptive therapy and calcitriol may be effective at preventing bone density loss after transplantation *[A]*. Considering the rates of bone loss after transplantation described in Annotation #3, "Patient on Chronic Glucocorticoid Therapy of Transplant Recipient," bone mineral density testing should be performed every 6 months to one year until bone mineral density is shown to be stable or improving on therapies for osteoporosis. Studies demonstrate that standard calcium and vitamin D supplementation, with or without calcitonin, are not able to prevent bone loss after transplantation. Other studies indicate that pharmacologic vitamin D preparations or intravenous bisphosphonates, such as pamidronate, or zoledronic acid, or oral bisphosphonates, such as alendronate or risedronate, are more likely to prevent bone loss after transplantation.

Alternative and Complementary Agents for Prevention and Treatment of Osteoporosis

There is conflicting data on a number of non-Food and Drug Administration (FDA) approved substances for possible use in prevention and treatment of osteoporosis. These include phytoestrogens, synthetic isoflavones such as ipriflavone, natural progesterone cream, magnesium, vitamin K and eicosapentaenoic acid. There are very limited data from randomized controlled trials of these agents for prevention or treatment of osteoporosis. A recently reported, multicenter, randomized trial of ipriflavone showed no significant effect on bone density or risk of vertebral fractures *[A]*.

Osteoporosis Treatment

Bisphosphonates have the strongest data showing risk reductions in both vertebral, hip, and other nonvertebral fractures. Other treatments include raloxifene (see SERM in this annotation) and calcitonin.

Parathyroid hormone 1-34 (teriparatide) (PTH) is used for patients at highest risk for fracture. It could be first-line therapy for those patients.

In addition to calcium, vitamin D, physical therapy, surgical repair, and radiologic intervention as appropriate, the therapies listed below may be used. Clinicians should be aware that patient compliance with adherence to osteoporosis therapy has been historically poor.

Gonadal Hormone Therapy

Female Gonadal Hormone Therapy

The use of supplemental estrogen in the immediate postmenopause has been well accepted in preventing the rapid loss of bone that occurs in this interval *[A]*.

Ultra-low estrogen supplementation has been shown to be effective in severely hypoestrogenic women in improving bone mass. Fracture data is pending.

Refer to the original guideline document for more information on female gonadal hormone therapy.

Male Gonadal Hormone Therapy

The bone loss associated with male hypogonadism is reversed by testosterone therapy at least partly via aromatization to estrogen. Testosterone therapy, although not FDA-approved for osteoporosis, seems a reasonable first therapeutic intervention in men symptomatic with hypogonadism who do not have contraindications to the use of testosterone therapy *[C]*, *[D]*.

Bisphosphonates

Treatment and Prevention of Osteoporosis in Postmenopausal Women

Alendronate has been shown to increase bone mineral density and reduce the incidence of vertebral, hip, and non-vertebral fractures in postmenopausal women having existing vertebral fractures, and those with low bone mineral density (approximately 2.1 SD below peak) compared to placebo (calcium and vitamin D).

Excellent clinical trial data based on BMD and bio-markers supports the use of oral bisphosphonates for preventing fractures in patients diagnosed with postmenopausal low bone density (osteopenia) or osteoporosis. The best clinical trials have been done with alendronate, risedronate, and ibandronate. [*Conclusion Grade I: See Conclusion Grading Worksheet B -- Annotation #13 (Bisphosphonates for Primary Osteoporosis) in the original guideline document*]. (See Appendix B, "Recommended Pharmacologic Agents" in the original guideline document.)

Refer to the original guideline document for more information.

Treatment of Osteoporosis in Men

Alendronate has been shown to increase bone mineral density at the spine, hip, and total body and prevents vertebral fractures and decreases in height for men with osteoporosis *[A]*.

Good clinical trial data support the use of alendronate for preventing bone loss in men diagnosed with osteoporosis. [*Conclusion Grade I: See Conclusion Grading Worksheet B -- Annotation #13 (Bisphosphonates for Primary Osteoporosis) in the original guideline document*].

Treatment and Prevention of Glucocorticoid-Induced Osteoporosis

Alendronate increases lumbar spine, femoral neck, trochanter, and total body bone mineral density in patients who require long-term (at least one year) glucocorticoid therapy at dosages of at least 7.5 mg daily *[A]*.

Risedronate has also been shown to increase bone mineral density in patients receiving glucocorticoid therapy. Treatment with risedronate 5 mg a day did have a trend of reduced fracture incidence *[A]*.

Clinical trial data suggests that oral bisphosphonates may reduce fracture risk in men and women diagnosed with glucocorticoid-induced bone loss. [*Conclusion Grade III: See Conclusion Grading Worksheet C -- Annotation #13 (Bisphosphonates for Glucocorticoid-Induced Bone Loss) in the original guideline document*].

In patients with high risk of fracture secondary to long-term glucocorticoid therapy, teriparatide may be considered a therapeutic option *[A]*.

Teriparatide is only approved for duration of two years. A gradual decrease in bone mass has been noted after discontinuation of teriparatide therapy; however, following therapy with a bisphosphonate has been shown to preserve the benefits *[M]*, *[R]*.

Post-transplantation

Solid organ transplantation of all types and allogeneic bone marrow transplantation are associated with rapid bone loss after transplantation. In addition, many patients develop significant bone loss before transplantation.

Several studies have shown that intravenous pamidronate *[A]* and zoledronate *[A]* may prevent bone loss after organ transplantation. A few small studies have evaluated oral bisphosphonate therapy in post-transplant patients *[A]*, *[B]*, *[R]*.

Bisphosphonates and the Risk of Osteonecrosis of the Jaw

The risk of development of osteonecrosis of the jaw (ONJ) in postmenopausal osteoporotic patients treated with oral or intravenous bisphosphonates appears to be very low, as only a small number of cases have been reported, most associated with alendronate therapy. Based on review of the published literature and unpublished data, the current risk estimate for ONJ in patients

with postmenopausal osteoporosis is between 1 in 10,000 and less than 1 in 100,000 patient-treatment years *[M]*. The pathophysiology of this condition is not known, but it may be associated with excessive suppression of bone turnover, decreased angiogenesis, or dental infection or trauma.

In summary, bisphosphonate-associated ONJ appears to occur most commonly in patients with multiple myeloma or breast or prostate cancer metastatic to the skeleton who receive frequent intravenous infusions of potent nitrogen-containing bisphosphonates. This disorder appears to be rare in postmenopausal women or men treated with oral bisphosphonates for osteoporosis. Jaw osteonecrosis may occur during treatment with intravenous or oral bisphosphonates, but 94% of cases in the largest series to date *[M]* occurred with intravenous zoledronic acid or pamidronate in cancer patients. Risk factors include cancer, frequent infusions of intravenous nitrogen-containing bisphosphonates, and dentoalveolar trauma or infection. Before beginning therapy with oral or intravenous bisphosphonates, patients should be referred for dental care to address dental issues. Bisphosphonate therapy should not be started until dental issues have been resolved. Treatment with systemic antibiotics and oral antibiotic rinses may help with pain and eventually lead to healing. Stopping bisphosphonate therapy may be prudent, as anecdotal evidence suggests that this may help in some cases. Aggressive dental surgery should generally be avoided.

Bisphosphonates and Risk of Atrial Fibrillation

Recent publications have suggested that at least some postmenopausal women taking oral or intravenous bisphosphonates for osteoporosis may be at increased risk of atrial fibrillation. The HORIZON Trial *[A]* demonstrated an unexpected mildly increased risk of serious atrial fibrillation. This was not seen in a subsequent trial of postmenopausal women following hip fracture that showed that zoledronic acid reduced fractures and mortality but did not show an increased incidence of atrial fibrillation in this older population at higher risk of atrial fibrillation *[A]*. Reanalysis of the Fracture Intervention Trial with alendronate and a retrospective review of risedronate data did not show an increased risk of atrial fibrillation *[A]*, *[NA]*. Conflicting data is reported from two separate population-based case control studies *[C]*. In light of the conflicting results from these studies, it is premature to stop oral or intravenous bisphosphonates in patients with postmenopausal osteoporosis due to concerns about atrial fibrillation. Patients who are currently on bisphosphonates are advised to continue their medication as prescribed and to direct any questions they have about their medication to their health care provider.

Selective Estrogen Receptor Modulator (SERM)

The only SERM approved for the prevention and treatment of osteoporosis is raloxifene.

The MORE trial was a large 3-year randomized placebo-controlled study in postmenopausal women with osteoporosis. Raloxifene showed an increase in BMD and reduced the risk of vertebral fractures. The risk of non-vertebral fractures did not differ between placebo and raloxifene. There was an

increased risk of venous thromboembolism compared with placebo (RR 3.1, 95% CI 1.5-6.2) *[A]*.

The CORE 4-year trial extension of 4,011 women continuing from MORE (7,705) showed no difference in overall mortality, cardiovascular events, cancer or nonvertebral fracture rates *[A]*.

In the STAR trial *[A]*, raloxifene was found comparable to tamoxifen for the prevention of invasive breast cancer. Thus, raloxifene appears to be the drug of choice for women with osteoporosis if the main risk is of spinal fracture and there is an elevated risk of breast cancer.

Calcitonin

Treatment of Osteoporosis in Postmenopausal Women

Nasal salmon-calcitonin 200 international units daily has shown a 33% risk reduction in new vertebral fractures compared with placebo (RR 0.67, 95% CI 0.47-0.97, p = 0.03). This occurred without significant effects on BMD. BMD measurements were not blinded to investigators and 59% (744) participants withdrew from the study early. Also, a dose response was not observed with respect to risk reduction of vertebral fractures *[A]*.

Post-transplantation

Several studies have shown that nasal spray calcitonin has little effect on prevention of bone loss after organ or bone marrow transplantation *[A]*.

Refer to the original guideline document for information on anabolic agents, strontium, combination therapy (estrogen and bisphosphonates); comparative trials; calcitriol-1 25-OH vitamin D; and alternative and complementary agents (phytoestrogens, ipriflavone, natural progesterone, magnesium, vitamin K, eicosapentaenoic and gamma-linolenic acid supplementation, and kampo formulae).

Alternative and Complementary Agents

Adherence to Medications for Bone Loss

Adherence (compliance + persistence) is a major problem with medications for bone loss. The literature suggests that 45% to 50% of patients on one of these agents have stopped them within one year *[B]*. Adherence to therapy was associated with significantly fewer fractures at 24 months *[B]*. The use of follow-up bone densitometry and bone markers has not been shown to improve adherence. Follow-up phone calls or visits have shown improvement in adherence *[R]*. Although not studied, a close relationship with a primary care provider who thoroughly discusses the rationale, risks and benefits of treatment most likely improves adherence significantly, especially if followed up by a phone call or visit. Several studies support weekly bisphosphonate dosing versus daily, and/or monthly dosing versus weekly to improve compliance *[A]*, *[B]*.

14. **Follow-Up Testing After Pharmacologic Intervention**

Key Points:

- Periodic follow-up central DXA on the same machine is recommended for following patients on pharmacologic therapy.
- The testing interval varies from 6 to 24 months depending on the clinical situations.

Sequential bone density testing using central DXA may be useful, and is generally recommended in monitoring drug therapy for the treatment of osteopenia or osteoporosis *[R]*. Ideally, such testing should be performed on the same machine as the pre-treatment bone density and no more than every 12 to 24 months. A frequency as often as every 6 to 12 months may be indicated in the case of glucocorticoid treated patients or those on suppressive doses of thyroid hormone. Other patients at risk for accelerated bone loss include women at early menopause or those who have discontinued estrogen and are not on another bone protective agent*. The lumbar spine and the total proximal femur have the highest reproducibility and are the preferred sites for monitoring therapy *[R]*. Changes in BMD should only be reported as significant if they exceed the "least significant change" for the DXA center *[C]*, *[R]*. Stability or increase in BMD indicates successful therapy. A significant decline in BMD may require further investigation.

A significant decrease in BMD on therapy may be due to:

- Poor drug adherence
- Improper medication administration technique in the case of bisphosphonates
- A missed secondary cause of osteoporosis (e.g., hyperparathyroidism, malabsorption)
- Inadequate calcium intake
- Untreated Vitamin D deficiency
- A true treatment failure due to the drug itself
- Malabsorption of orally administered drugs

Further follow-up BMD testing after stability or improvement over three to four years has been demonstrated is recommended by most experts. No study has been done as to whether follow-up BMD testing on therapy enhances fracture risk reduction but it may affect patient adherence to therapy *[A]*. Therapy should not be withheld if follow-up bone density testing is not available.

*Medicare provides coverage for bone densitometry with central DXA every two years to monitor osteoporosis therapy *[NA]*.

Definitions:

Conclusion Grades:

Grade I: The evidence consists of results from studies of strong design for answering the question addressed. The results are both clinically important and

consistent with minor exceptions at most. The results are free of any significant doubts about generalizability, bias, and flaws in research design. Studies with negative results have sufficiently large samples to have adequate statistical power.

Grade II: The evidence consists of results from studies of strong design for answering the question addressed, but there is some uncertainty attached to the conclusion because of inconsistencies among the results from the studies or because of minor doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from weaker designs for the question addressed, but the results have been confirmed in separate studies and are consistent with minor exceptions at most.

Grade III: The evidence consists of results from studies of strong design for answering the question addressed, but there is substantial uncertainty attached to the conclusion because of inconsistencies among the results of different studies or because of serious doubts about generalizability, bias, research design flaws, or adequacy of sample size. Alternatively, the evidence consists solely of results from a limited number of studies of weak design for answering the question addressed.

Grade Not Assignable: There is no evidence available that directly supports or refutes the conclusion.

Classes of Research Reports:

A. Primary Reports of New Data Collection:

Class A:

- Randomized, controlled trial

Class B:

- Cohort study

Class C:

- Non-randomized trial with concurrent or historical controls
- Case-control study
- Study of sensitivity and specificity of a diagnostic test
- Population-based descriptive study

Class D:

- Cross-sectional study
- Case series
- Case report

B. Reports that Synthesize or Reflect upon Collections of Primary Reports:

Class M:

- Meta-analysis
- Systematic review
- Decision analysis
- Cost-effectiveness analysis

Class R:

- Consensus statement
- Consensus report
- Narrative review

Class X:

- Medical opinion

CLINICAL ALGORITHM(S)

A detailed and annotated clinical algorithm is provided for Diagnosis and Treatment of Osteoporosis.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is classified for selected recommendations (see "Major Recommendations").

In addition, key conclusions contained in the Work Group's algorithm are supported by a grading worksheet that summarizes the important studies pertaining to the conclusion. The type and quality of the evidence supporting these key recommendations (i.e., choice among alternative therapeutic approaches) is graded for each study.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Appropriate recognition, prevention, and treatment of osteoporosis and subsequent decrease in bone loss and fracture risk and increase in bone health
- Improved diagnostic and therapeutic follow-up of adults presenting with a history of low-impact fracture
- Increased evaluation for osteoporosis risk factors in all adults presenting for a preventive visit

POTENTIAL HARMS

Side Effects of Medication

- *Calcium*. Oversupplementation of calcium may be associated with an increased risk of kidney stones and vascular calcification.
- *Raloxifene*. Hot flashes and leg cramps, and increased risk of venous thromboembolic events are reported side effects of raloxifene.
- *Bisphosphonates*. Oral bisphosphonate preparations have the potential to cause esophagitis, abdominal pain, esophageal ulcer, diarrhea, musculoskeletal pain, acid regurgitation, dyspepsia, dysphagia, flu-like symptoms (rare), atrial fibrillation, and jaw osteonecrosis (on rare occasions).
- *Calcitonin*. Nausea, flushing, rhinitis with nasal spray
- *Estrogen*. Bloating; breast tenderness; uterine bleeding; increased risk of myocardial infarction, stroke, increased risk of myocardial infarction, stroke, venous thrombosis or pulmonary embolism, and breast cancer

See Appendix B of the original guideline document for a more complete list of adverse drug reactions.

CONTRAINDICATIONS

CONTRAINDICATIONS

- *Alendronate (Fosamax®)*. Contraindications include abnormalities of the esophagus which delay esophageal emptying, inability to stand or sit upright for at least 30 minutes, hypersensitivity, and uncorrected hypocalcemia. It is not recommended for patients with creatinine clearance (CrCl) equal to or less than 35 mL/min.
- *Risedronate (Actonel®)*. Contraindications include inability to stand or sit upright for at least 30 minutes, hypersensitivity, and uncorrected hypocalcemia. It is not recommended for patients with CrCl equal to or less than 30 mL/min.
- *Ibandronate (Boniva®)*. Contraindications include uncorrected hypocalcemia, inability to stand or sit upright for at least 60 minutes, and hypersensitivity. It is not recommended for patients with CrCl equal to or less than 30 mL/min.
- *Zoledronic acid*. Contraindications include hypersensitivity to zoledronic acid or any of its excipients and uncorrected hypocalcemia. It is not recommended for patients with creatinine clearance less than 35 mL/min.
- *Raloxifene (Evista®)*. Contraindications include pregnancy, history of venous thromboembolism, hypersensitivity, and nursing women.
- *Teriparatide (Forteo®)*. Contraindications include Paget's disease, prior therapeutic radiation therapy involving the skeleton, bone metastases or history of skeletal malignancies, metabolic bone disease (other than osteoporosis), hypercalcemia, pregnant and nursing women, unexplained elevated alkaline phosphatase, hypersensitivity, and pediatric population or young adults with open epiphyses.
- *Calcitonin-salmon (Miacalcin® and Fortical® nasal spray)*. Contraindications include hypersensitivity.
- *Estrogens*. Contraindications include pregnancy; history of thromboembolic disorders; breast cancer (except appropriately selected patients treated for metastatic disease); estrogen dependent neoplasia; undiagnosed abnormal vaginal bleeding; hypersensitivity; liver dysfunction or disease, active or recent (within one year); and stroke or myocardial infarction.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- This clinical guideline is designed to assist clinicians by providing an analytical framework for the evaluation and treatment of patients, and is not intended either to replace a clinician's judgment or to establish a protocol for all patients with a particular condition. A guideline will rarely establish the only approach to a problem.
- This clinical guideline should not be construed as medical advice or medical opinion related to any specific facts or circumstances. Patients are urged to consult a health care professional regarding their own situation and any specific medical questions they may have.
- There are very limited data from randomized controlled trials of alternative and complementary agents for prevention or treatment of osteoporosis.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Once a guideline is approved for general implementation, a medical group can choose to concentrate on the implementation of that guideline. When four or more groups choose the same guideline to implement and they wish to collaborate with others, they may form an action group.

In the action group, each medical group sets specific goals they plan to achieve in improving patient care based on the particular guideline(s). Each medical group shares its experiences and supporting measurement results within the action group. This sharing facilitates a collaborative learning environment. Action group learnings are also documented and shared with interested medical groups within the collaborative.

Currently, action groups may focus on one guideline or a set of guidelines such as hypertension, lipid treatment, and tobacco cessation.

The following detailed measurement strategies are presented to help close the gap between clinical practice and the guideline recommendations.

Priority Aims and Suggested Measures

1. Increase the evaluation for osteoporosis risk factors in all adults presenting for a preventive visit.

   Possible measures for accomplishing this aim:

   a. Percentage of patients presenting for a preventive visit with documentation of assessment of risk factors for osteoporosis.
   b. Percentage of patients at risk for fracture presenting for a preventive visit who are offered bone densitometry.

c. Percentage of patients presenting for a preventive visit with documentation that vitamin D and calcium issues have been addressed.

2. Improve the treatment of patients diagnosed with osteoporosis.

   Possible measures for accomplishing this aim:

   a. Percentage of patients aged 50 and older with a diagnosis of osteoporosis prescribed pharmacologic therapy within 12 months.
   b. Percentage of patients with a diagnosis of osteoporosis who have received documented activity education or a referral for activity counseling within the most recent 36 months.

3. Improve diagnostic and therapeutic follow-up of adults presenting with a history of low-impact fracture.

   Possible measures of accomplishing this aim:

   a. Percentage of adults presenting with a history of low-impact fragility fracture who have had bone densitometry.
   b. Percentage of postmenopausal women and men with a history of low-impact fragility fracture evaluated and offered treatment for osteoporosis.
   c. Percentage of adults with a history of low-impact fragility fracture offered treatment for osteoporosis.
   d. Percentage of adults with a history of low-impact fragility fracture with documentation of discussion with a health care provider of osteoporosis risk offered treatment for osteoporosis.
   e. Percentage of adults with a low-impact fragility fracture on therapy for osteoporosis with documentation of calcium and vitamin D intake meeting the minimum thresholds for treatment.
   f. Percentage of patients aged 50 or older treated for a hip, spine, or distal radial fracture with documentation of communication with the physician managing the patient's ongoing care that a fracture occurred and that the patient was or should be tested or treated for osteoporosis.

At this point in development for this guideline, there are no specifications written for possible measures listed above. Institute for Clinical Systems Improvement (ICSI) will seek input from the medical groups on what measures are of most use as they implement the guideline. In a future revision of the guideline, one or two measurement specifications may be included.

IMPLEMENTATION TOOLS

Clinical Algorithm
Patient Resources
Pocket Guide/Reference Cards

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Institute for Clinical Systems Improvement (ICSI). Diagnosis and treatment of osteoporosis. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2008 Sep. 67 p. [179 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2002 Aug (revised 2008 Sep)

GUIDELINE DEVELOPER(S)

Institute for Clinical Systems Improvement - Private Nonprofit Organization

GUIDELINE DEVELOPER COMMENT

Organizations participating in the Institute for Clinical Systems Improvement (ICSI): Affiliated Community Medical Centers, Allina Medical Clinic, Altru Health System, Aspen Medical Group, Avera Health, CentraCare, Columbia Park Medical Group, Community-University Health Care Center, Dakota Clinic, ENT Specialty Care, Fairview Health Services, Family HealthServices Minnesota, Family Practice Medical Center, Gateway Family Health Clinic, Gillette Children's Specialty Healthcare, Grand Itasca Clinic and Hospital, HealthEast Care System, HealthPartners Central Minnesota Clinics, HealthPartners Medical Group and Clinics, Hutchinson Area Health Care, Hutchinson Medical Center, Lakeview Clinic, Mayo Clinic, Mercy Hospital and Health Care Center, MeritCare, Mille Lacs Health System, Minnesota Gastroenterology, Montevideo Clinic, North Clinic, North Memorial Care System, North Suburban Family Physicians, Northwest Family Physicians, Olmsted Medical Center, Park Nicollet Health Services, Pilot City Health Center, Quello Clinic, Ridgeview Medical Center, River Falls Medical Clinic, Saint Mary's/Duluth Clinic Health System, St. Paul Heart Clinic, Sioux Valley Hospitals

and Health System, Southside Community Health Services, Stillwater Medical Group, SuperiorHealth Medical Group, University of Minnesota Physicians, Winona Clinic, Ltd., Winona Health

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GUIDELINE COMMITTEE

Committee on Evidence-Based Practice

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Christine Simonelli, MD receives research grant support from Novartis, Eli Lilly, Roche and GSK and serves as a consultant to Amgen, Novartis, Roche and Merck, and is a DSMB member for Amgen.

Bart Clarke, MD, is a DSMB member for Amgen and is a consultant to GSK.

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John Schousboe, MD, receives research grant support from Novartis and is a consultant to Merck.

No other work group members have potential conflicts of interest to disclose.

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GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Diagnosis and treatment of osteoporosis. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2006 Jul. 64 p.

GUIDELINE AVAILABILITY

Electronic copies: Available from the Institute for Clinical Systems Improvement (ICSI) Web site.

Print copies: Available from ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; Web site: www.icsi.org; e-mail: icsi.info@icsi.org.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Diagnosis and treatment of osteoporosis. Executive summary. Bloomington (MN): Institute for Clinical Systems Improvement, 2008 Sep. 1 p. Electronic copies: Available from the Institute for Clinical Systems Improvement (ICSI) Web site.
- ICSI pocket guidelines. May 2007 edition. Bloomington (MN): Institute for Clinical Systems Improvement, 2007.

Print copies: Available from ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; Web site: www.icsi.org; e-mail: icsi.info@icsi.org.

PATIENT RESOURCES

The following is available:

- Diagnosis and treatment of osteoporosis. Bloomington (MN): Institute for Clinical Systems Improvement, 2006 July 18 p.

Electronic copies: Available from the Institute for Clinical Systems Improvement (ICSI) Web site.

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NGC STATUS

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